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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,425	11/24/2000	Oren Becker	24460	1582
20529	7590	07/18/2007		
NATH & ASSOCIATES 112 South West Street Alexandria, VA 22314			EXAMINER LIN, JERRY	
			ART UNIT 1631	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/718,425	BECKER ET AL.	
	Examiner	Art Unit	
	Jerry Lin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 May 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 18-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17, 22 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 16, 2007 has been entered.

Applicants' arguments, filed May 16, 2007, have been fully considered and they are deemed to be persuasive. However, upon consideration of the amendments, the following rejections are newly applied as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-17, 22 and 23 are under examination.

Claims 18-21 are withdrawn as being drawn to an unelected invention.

Claim Objections

2. Claim 1 is objected to because of the following informalities: In step b), line 1, the word "provide" should be "provided". In step e), substep v), "position/s" is confusing and unconventional. The Examiner recommends amending it to "position(s)". Similarly,

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in step g), the Examiner recommends amending "structure/s" to "structure(s)".

Appropriate correction is required.

Claim 17 is objected to because of the following informalities: the tense of the word "stabilized" should be "stabilizes". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-17, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, step e) ii), it is unclear as to what is being calculated. One interpretation is that the delta E between the entire predetermined protein/peptide and each mutated residue (i.e., the whole protein vs. a residue) or between each mutated residue and the residue in that position of the predetermined protein/peptide (i.e., residue vs. residue).

Claim 1, step f), recites the limitation "the predefined 3D structure" in line 4. Instant claim 15 also recites this term in line 3. There is insufficient antecedent basis for this limitation in the claims. While the instant claim 1 does recite a "3D structure of a predetermined protein or peptide," the instant claims do not have a prior reference to a "predefined 3D structure".

The term "essentially the same" in claim 1, line 4, is a relative term which renders the claim indefinite. The term "essentially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not teach any clear standard of determining if the biological activity is essentially the same.

The term "substantially water" in claim 6 is a relative term, which renders the claim indefinite. The term "substantially water" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not teach any clear standard of the amount of water needed in a solvent in order for it to be substantially water.

Claim 22 recites the limitation "the native amino acid sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim. This term was not mentioned previously in the instant claim from the claims from which it depends.

Claim 23 recites the limitation "said processing means" in step f). There is insufficient antecedent basis for this limitation in the claim. While the instant claims do mention "a processor", the instant claims do not mention the limitation "processing means" previously in the instant claim.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

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Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-17, 22 and 23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The instant claims are drawn to a process involving the judicial exception of a computational algorithm. Claims drawn to a judicial exception is non-statutory unless the claims include a practical application of that judicial exception as evidenced by a physical transformation of the claimed invention, or if the claimed invention produces a useful, tangible and concrete final result. In the instant claims, there is no physical transformation by the claimed invention, thus the Examiner must determine if the instant claims produce a useful, tangible, and concrete final result.

In determining if the instant claims have a useful, tangible, and concrete final result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a final result that is specific, substantial, and credible. For a claim to be "tangible," the claim must set forth a practical application of the invention that produces a real-world final result. For a claim to be "concrete," the process must have a final result that can be substantially repeatable or the process must substantially produce the same result again. Furthermore, the claim must recite a useful, tangible, and concrete final result in the claim itself, and the claim must be limited only to statutory embodiments. Thus, if the claim is broader than the statutory embodiments of the claim, the Examiner must reject the claim as non-statutory.

The instant claims do not produce a useful, tangible, and concrete final result. The useful, tangible, and concrete requirement requires that the claim must set forth a

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practical application of the mathematical algorithm to produce a real-world result. The instant claims are drawn to a method of predicting at least one amino acid sequence. It is noted that the last step, g), is an optional step and is not given patentable weight. The last required step of the claims is drawn to expending the reduced representation. This final required step does not indicate that a result has necessarily been produced. Thus the instant claims do not require that a result must be produced. Since there is no final result in the claims, the instant claims do not include a useful, tangible, and concrete final result. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display or a memory or another computer on a network, or to a user, or by including a physical transformation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-5, 9-17, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (Protein Science (1996) Volume 5, pages 895-903) and further in view of Herzyk et al. (Proteins) Volume 17, pages 310-324).

The instant claims are drawn to a method of predicting an amino acid sequence by providing a coordinate set representing the backbone of a 3D structure, constructing a reduced virtual representation for the 3D structure, determining the amino acid positions along the 3D structure, constructing an initial amino acid sequence, randomly selecting one or more positions along the sequence and applying a Monte-Carlo simulation, and expanding the reduced representation.

Regarding claims 1-5, 9-17, 22 and 23, Dahiyat et al. teaches protein design automation. Specifically they teach "We have conceived and implemented a cyclical protein design strategy that couples theory, computation, and experimental testing. The combinatorially large number of possible sequences and the incomplete understanding of the factors that control protein structure are the primary obstacles in protein design. Our protein design automation algorithm objectively predicts protein sequences likely to achieve a desired fold. Using a rotamer description of the side chains, we implanted a fast discrete search algorithm based on the Dead End Elimination Theorem to rapidly find the globally optimal sequence in its optimal geometry from the vast number of possible solutions. Rotamer sequences were scored for steric complementarity using a van der

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Waals potential. A Monte Carlo search was then executed, starting at the optimal sequence in order to find other high-scoring sequences. As a test of the design methodology, a high scoring sequences were found for the buried hydrophobic residues of a homodimeric coiled coil base on GCN4-p1. The corresponding peptides were synthesized and characterized by DC spectroscopy and size exclusion chromatography.

... A quantitative structure activity relation analysis was performed on the designed peptides, and a significant correlation was found with surface area burial. Incorporation of the buried surface area potential in the scoring of sequences greatly improved the correlation between predicted and measured stabilities and demonstrated experimental feedback in a complete design cycle.” (Abstract). Specifically, Dahiyat also teaches that the PDA side-chain selection algorithm requires as input a backbone structure defining the desired fold. Also taught is that “using a rotamer description of side chains, an optimal sequence for a backbone can be found by screening all possible sequences of rotamers, where each backbone position can be occupied by each amino acid and all its possible rotameric states.” (page 896). (This corresponds to steps (a) through (d) of claim 1.) Also taught is “following DEE optimization, a rank-ordered list of sequences is generated by a Monte Carlo search in the neighborhood of the DEE solution. . . random position are changed to other rotamers, and the new energy is calculated. If the new sequence energy meets the Boltzmann criteria for acceptance, it is used as the starting point for another jump. . . after a predetermined number of jumps, the best scoring sequences are output as a rank-ordered list.” (Page 897). (This corresponds to step (e) of claim 1.) Also taught is that simpler structure measure, such as buried atoms, were

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used to resolve the structure of the amino acid. (page 899). (This corresponds to step (f) of claim 1.) Dahiyat et al. also teach using hydrophobic and hydrophilic positions to determine the structure (page 897). In regards to claims 8, 10, 11, since all positions are selected from the entire group of amino acids, these claims are fully anticipated. In regard to claim 23, Dahiyat et al. teaches using a computational method that would require use of a computer with an input apparatus, multiple memories, and a processor (page 901, right column).

However, Dahiyat et al. does not teach representing a protein wherein each amino acid has a backbone portion and side chain portion, where the backbone portion is represented by a single sphere and the side chain of each amino acid is represented by one to two additional spheres.

Regarding claim 1, Herzyk et al. teach representing a protein wherein each amino acid has a backbone portion and side chain portion, where the backbone portion is represented by a single sphere and the side chain of each amino acid is represented by one to two additional spheres. (Abstract; page 312 and throughout. See also specification at page 9, lines 3-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the representation taught by Herzyk et al. with the method of Dahiyat et al. to gain the benefit of using less computer time for generating a single structure. Given the large degree of complexity of proteins, generating the structure of a protein requires a large amount of time and computer processing power. This is especially true of using an all-atom representation of a protein. Herzyk et al. teaches a

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way of representing a protein that uses less computer time (abstract). Thus one of ordinary skill in the art seeking to determine the structure of a protein as quickly as possible using the computationally intensive method of Dahiyat et al., would be motivated to use Herzyk et al.'s method to reduce computer time needed for processing.

9. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (Protein Science (1996) Volume 5, pages 895-903) and further in view of Herzyk et al. (Proteins) Volume 17, pages 310-324) as applied to claim 1, etc. above, and further in view of Hurley et al. (JMB Vol. 224, 1992, pages 1143-1159).

Dahiyat et al. and Herzyk et al. are applied as above.

However, neither Dahiyat et al. nor Herzyk et al. teaches that the solvent is substantially water.

Regarding claims 6-8, Hurley et al. teaches design and structural analysis of alternative hydrophobic core packing arrangements in bacteriophage T4 lysozyme. Particularly, they teach, "in order to calculate stability changes in aqueous solution, the changes in free energies of transfer of the folded and unfolded states between water and vacuum must be obtained." (Page 1146).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teaching of Dahiyat et al., Herzyk et al., and those of Hurley et al. As Hurley et al. teach, it would have been obvious to determine the structure of an amino acid in water because it would have allowed for the calculation of stability

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change. Also, water would have been a common solvent for the amino acid structures to be found in nature, and therefore would have been obvious to use as it would have allowed for the closest approximation to nature. Furthermore, water would have been obvious solvent due to its neutral pH, low cost, and easy availability.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561.

The examiner can normally be reached on 10:00-6:30, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JL/

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